

Evidence-Based Update on Treatment Armamentarium for Crohn's Disease

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Summary

Crohn's disease is an example of a disease for which biologic injectable therapy is rapidly expanding. Biologics are going to take a larger and larger part of managed care's pharmacy spending. With the exponentially exploding use of biologics, managing their use is important for managed care's financial security and longevity.

Key Points

- Crohn's disease is a common inflammatory bowel disorder which can be used to examine the use of biologics within the context of managed care.
- Although immunosuppressant use has increased over the past 25 years, intestinal resections have not significantly decreased.
- An increasing number of biologics are being approved for use in Crohn's disease.
- As biologic use and availability increases, managed care must be aware of the issues that drive the increasing use of these agents and ways to control their use.

CROHN'S DISEASE, A CHRONIC INFLAMMATORY disorder of the gastrointestinal tract, is a relatively common disorder with a wide spectrum of severity. It affects approximately 5 percent of the U.S. population (~500,000 people).¹ The disease typically strikes when patients are in the prime of life—when disability can be devastating.² It mainly affects people between 15 and 35 years of age, with a smaller incidence peak later in life.^{3,4}

The direct medical costs of Crohn's disease in the U.S. are estimated at \$2 billion; more than half of this total is for hospitalization.⁵ In a review of an integrated claims database, direct charges (based on reimbursement) and utilization of resources were reported for 607 Crohn's patients. Approximately 25 percent of patients accounted for 80 percent of the total charges.⁶ The patients with the highest medical costs were those that required hospitalization followed by those who required steroid or immunomodulatory therapy but not hospitalization. Surgical procedures accounted for the largest percentage of hospital costs.⁷

The etiology of Crohn's disease is unknown. The current theory is that a genetic predisposition combines with an environmental factor and a dysregulated immune system to result in the inability to control

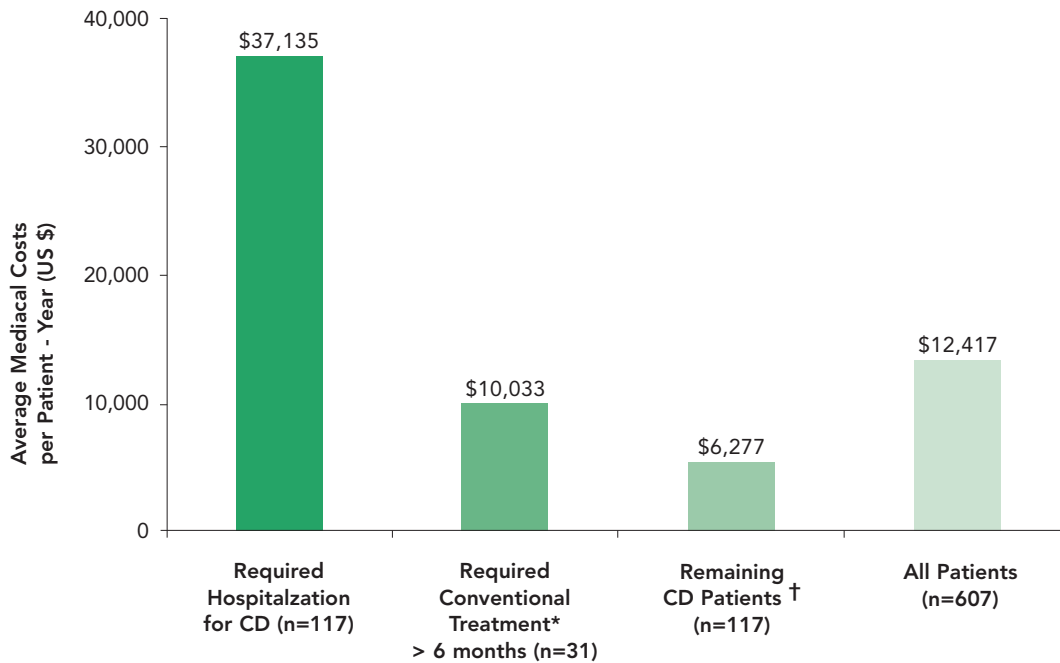
mucosal inflammation. Smokers are at greater risk for developing the disease, having more aggressive disease, and requiring more aggressive therapy.⁸ Recurrence following surgery is more frequent and hastened in patients who smoke.⁹

Exhibit 2 illustrates the definitions for the levels of Crohn's disease severity.² Identifying whether the disease is mild, moderate, or severe is a key step in selecting therapy. Refractory disease has been defined as those patients who require prolonged steroids, repeated hospitalizations, repeated surgeries or the initiation of biologics and immunomodulators to control disease activity, and initially do well on a tumor necrosis factor (TNF) inhibitor but then lose treatment response.¹⁰

One study retrospectively and prospectively assessed long-term evolution of Crohn's disease, and determined predictive factors and prognostic implications of this evolution. Six hundred forty-six patients with Crohn's disease were studied for more than five years retrospectively. Sixty percent developed a stricturing or penetrating complication.¹¹ The twenty year actuarial rates of inflammatory, stricturing, and penetrating disease were 12 percent, 18 percent, and 70 percent, respectively.¹¹ As illustrated in Exhibit 3, most patients with Crohn's will

Exhibit 1: Annual Medical Costs for Patients With CD

Approximately 25% of patients accounted for 80% of the total charges



*Steroid and/or immunomodulator;

†All patients not requiring hospitalization and not requiring steroid and/or immunomodulator therapy > 6 months.
Feagan BG et al. *Am J Gastroenterol.* 2000;95:1955-1960.

eventually develop a stricturing or a perforating complication.¹¹

Therapy for Crohn’s disease has evolved over the years (Exhibit 4). Initial treatments were aspirin and antibiotics. The use of antimetabolites and steroids

began in the 1970s. The development of injectable monoclonal antibodies has transformed the treatment of Crohn’s disease and many other autoimmune diseases. Infliximab and adalimumab are both FDA approved for treating Crohn’s disease. Many of

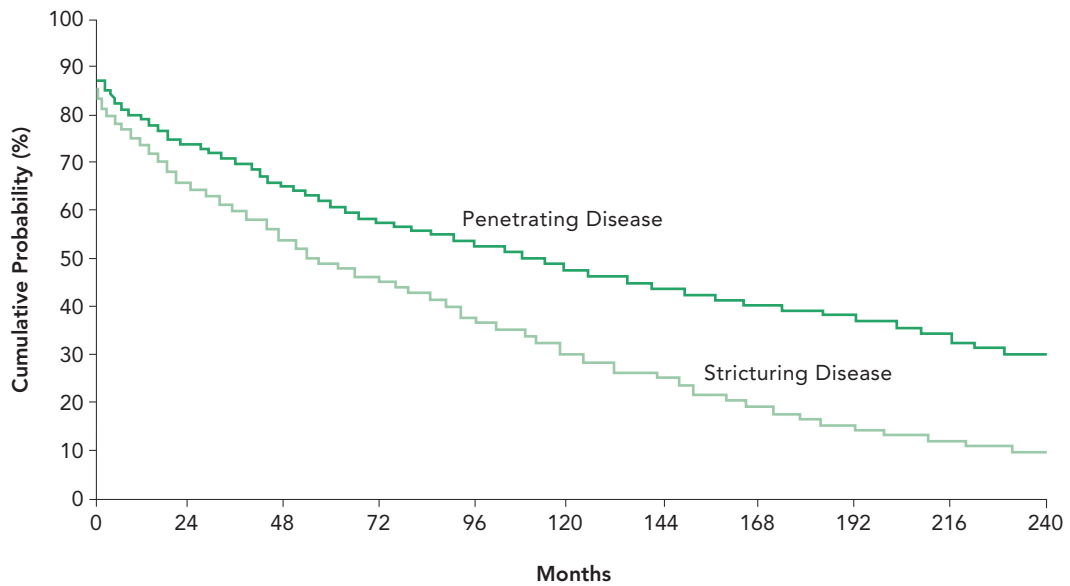
Exhibit 2: Characteristics of CD Severity

Mild Disease	Moderate Disease	Severe Disease
Minimal abdominal pain	Abdominal pain	Severe abdominal pain with nausea and vomiting
≤ 4 liquid bowel movements daily	Frequent loose-to-liquid bowel movements daily; blood in stool	> 10 bowel movements daily; ongoing blood in stool; obstructions
Lack systemic symptoms of inflammation (eg, fever, weight loss, inflammatory mass, ulcers anemia)	Systemic symptoms of inflammation	Systemic symptoms of inflammation
No symptoms outside the digestive tract (eg, arthritis, eye inflammation, skin disorders)	No symptoms outside the digestive tract	Symptoms outside the digestive tract

Hanauer SB et al. *Am J Gastroenterol.* 2001;96(3):635-643.

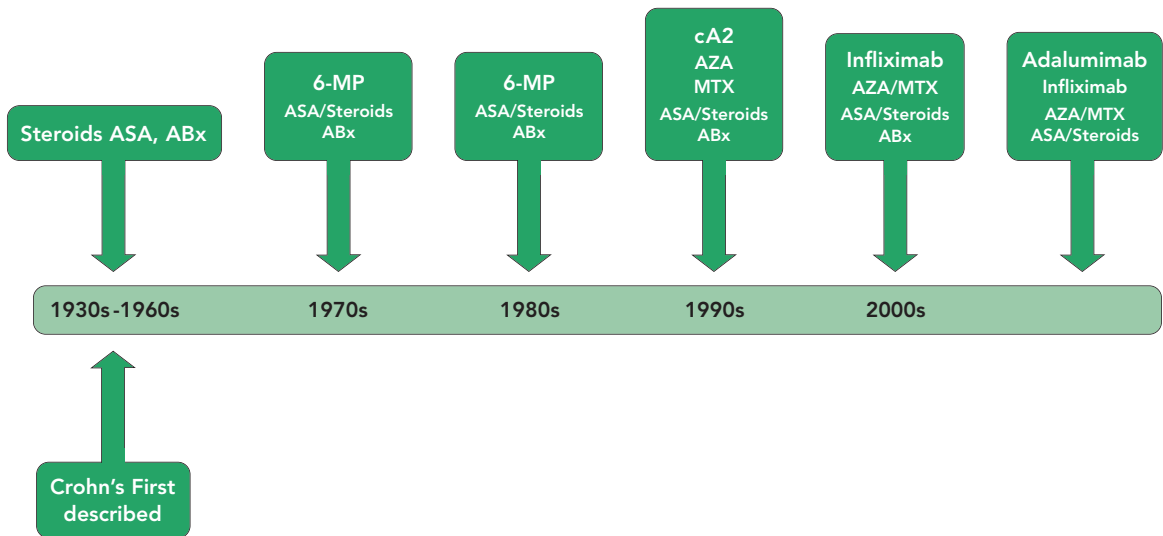
Exhibit 3: Longterm Course of CD: Probability of Remaining Free of Complications

Most Patients With CD Will Eventually Develop a Strictureing or a Perforating Complication



Penetrating disease = occurrence of fistula; strictureing disease = narrowing of the bowel leading to obstruction.
Cosnes J et al. *Inflamm Bowel Dis.* 2002;8:244-250.

Exhibit 4: Evolution of Crohn's Treatment



the medications that are commonly used in the treatment of this disease are not FDA approved for this indication (Exhibit 5).

Conventional therapy for this disease includes rectal and systemic use of steroids. Compliance and side effects can be an issue with these agents. Budesonide is FDA-approved at 9 mg/day for induction of remission in mild-to-moderate CD

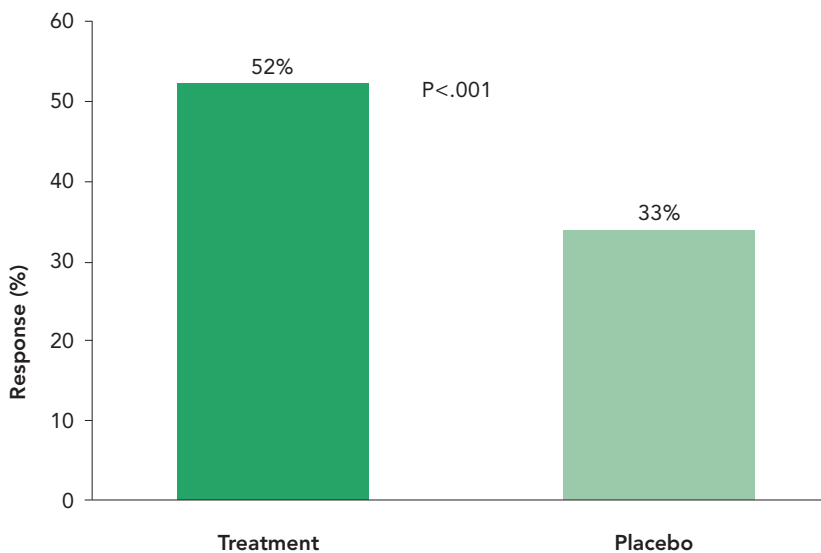
and maintenance of remission for 20 weeks. It is unclear if the majority of patients still receiving this agent can maintain clinically quiescent disease after 2 years.¹² Systemic corticosteroids (i.e., prednisone, hydrocortisone, methylprednisolone) are used after rectal steroids fail.^{13,14} Their use for longer than 3 months is inappropriate given their adverse effect profile.

Exhibit 5: Approved/Not Approved Drugs for the Treatment of Crohn's Disease

Drug	Approved	Not Approved
Infliximab	x	
Budesonide	x	
Prednisolone		x
Mesalamine		x
Antibiotics		x
Antimetabolites		x
Natalizumab		x
Adalimumab	x	
Sargramostim		x
Thalidomide		x
Etanercept		x

**Exhibit 6: GAIN
Remissions and Response Rates in Previous Infliximab Nonresponders**

Remission* rate of 21% was seen with treatment, vs 7% with placebo (P<.01)
Responder* rate illustrate below



*Remission (CDAI score < 150) at week 4; response (decrease in CDAI score ≥ 70 points) at week 4.
Sandborn WJ. *Am J Gastroenterol.* 2006;101:S1147. Abstract.

Antibiotics (e.g., broad-spectrum agents metronidazole and ciprofloxacin) are successful as first-line induction therapy in patients with disease predominantly limited to the colon and those with perianal

fistulas.¹⁵ There is concern over the overuse of these agents and possible increases in antibiotic resistance.

There is some data with aminosalicylates (5-ASA, mesalamine) that suggest effectiveness for mild-to-

moderate CD in patients with predominantly colonic disease.¹⁶ However; studies suggest the majority of patients do not receive any substantial therapeutic benefit.¹⁷

The immunomodulators used for this disease include the antimetabolites (6-MP or its prodrug azathioprine [AZA]) and methotrexate (MTX). Use of these agents is considered the standard of care. In controlled trials, these agents have been shown to induce and maintain remission in patients with severe inflammatory disease and fistulas.² However, up to 10 percent of patients do not tolerate the antimetabolites, and their use requires regular blood count monitoring for hematologic derangements.² Both azathioprine and methotrexate can cause significant long term adverse effects. Although immunosuppressant use for Crohn's disease increased significantly over the past 25 years, intestinal resections have not significantly decreased.¹⁸

Infliximab, a chimeric antibody to TNF-, was the first biologic approved by the FDA for treatment of Crohn's disease. It is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.¹⁹ It is also indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's.¹⁹ In small, relatively short term studies, infliximab is effective in decreasing the annual incidence of all surgeries (38%, $P < .01$); GI surgeries (18%, $P < .05$); endoscopies (43%, $P < .01$); ED visits (66%, $P < .05$); all outpatient visits (16%, $P < .05$); outpatient GI visits (20%, $P < .01$); all radiologic examinations (12%, $P < .01$); and plain films (13%, $P < .01$) in patients with refractory disease.²⁰ With infliximab, a scheduled regimen appears to provide more benefit than intermittent treatment of disease flares. In the 10 mg/kg scheduled group of the ACCENT 1 trial, a greater proportion of patients had complete mucosal healing at week 54 ($P = .041$) compared with intermittent therapy.²¹ The scheduled infliximab group also had a lower proportion of patients who developed antibodies and fewer disease-related hospitalizations ($P = .014$).²¹ Scheduled patients had fewer disease-related surgeries ($P = .01$).²¹

There appears to be a significant loss of treatment response occurring after one to two years of infliximab therapy. The reason for this is unknown. In one study, after 24 months of therapy, 77 percent of the patients had lost a treatment response.²² Regression analysis showed that loss of treatment response asso-

ciated with 29 percent higher annual total treatment costs and 29 percent higher disease-related costs than those who remained in remission ($P < .01$).²² In a lifetime of a chronic illness, we do not yet understand what the long term benefits are of a fifty-two week or shorter remission.

Because response to infliximab appears to fade, providers then look to switch to another biologic agent. The data for response to a second or even third biologic are limited. One agent, adalimumab, is approved for use in patients who have failed infliximab.

Adalimumab is a fully human anti-TNF antibody that recently received approval for use in Crohn's disease. It is indicated for reducing signs and symptoms of Crohn's and for inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy, or if they have lost response to, or are intolerant to infliximab.²³

A small trial showed that patients who become intolerant to infliximab can be treated with adalimumab and achieve a response (54%).²⁴ GAIN was an open label study, which studied adalimumab 160 mg followed by 80 mg at week two in 325 patients with active inflammatory disease who lost response to, or were intolerant of infliximab. Exhibit 6 illustrates the results of this study.²⁵ There was a response rate of 52 percent with treatment versus 33 percent with placebo ($P < .01$) and a 21 percent remission rate with treatment versus a rate of 7 percent in the placebo group ($P < .05$).²⁵

There are side effects with the TNF inhibitors. The most common adverse effects are upper respiratory infections, headache, cough, and arthralgias. Less common reactions include infusion reactions, serious infections, injection site reactions, antibodies to infliximab (10 to 30 percent), and antibodies to adalimumab (1 to 3 percent).^{19,23} Antibodies develop in patients treated with many of the biologic products. Why this occurs and the clinical significance are unknown. Not every patient produces the same antibodies nor the same volume, frequency, and intensity. The development of antibodies does seem to impact the duration of effect of some biologics. Rare adverse effects with the TNF inhibitors include reactivation of tuberculosis, opportunistic infections, lymphoma, demyelinating disorders, and exacerbation of heart failure.^{19,23}

In the future, we can expect approval of several new biologics for the treatment of Crohn's disease. These include new anti-TNF inhibitors (certolizumab pegol), anti-inflammatory cytokines and receptors (IL-11, IL-6R), adhesion molecule inhibitors (natalizumab, MLN-02), Th1 polarization inhibitors (anti-

IL-12 and anti-IFN- γ), and innate immunity activators, such as the colony stimulating factor sargramostim (rhGM-CSF).²⁶ Early data looking at clinical response and remission in short term studies with certolizumab pegol and natalizumab have shown promise.^{26,27}

Natalizumab was initially approved by the FDA in November 2004 for treatment of multiple sclerosis, but was withdrawn by the manufacturer in February 2005, after three patients in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML). Although rare, this is a serious and irreversible adverse effect.²⁸ Two of the reported cases were fatal. Based on this information, the FDA put clinical trials of the drug on hold in February 2005. FDA allowed a clinical trial of Tysabri to resume in February 2006, following a re-examination of the patients who had participated in the previous clinical trials, confirming that there were no additional cases of PML. In June of 2006, the FDA approved resumed marketing of natalizumab with a special restricted distribution program.²⁹

Because of the exponential growth of biologics, managed care needs to be aware of several trends or creeps that occur with biologic injectable therapy. There are seven creeps that will make or break a health plan financially. The first creep is dosage. With these agents, dosage increases over time. Frequency of dosing also increases. It may increase from once a month to every two weeks to weekly. A third factor increasing use is that biologic therapies are being initiated earlier in the disease process. The fourth factor is that patients are continuing on therapy beyond the point of benefit. The fifth factor is the expansion of FDA approved indications. The sixth factor is the off-label use. Once an agent is available on a formulary, it gets used for many indications other than those for which it is FDA approved. The last factor is the mode of administration—changing from intravenous to intramuscular to oral use, which makes the biologics easier to give.

There are a few more concepts that individuals in managed care need to understand about biologics in order to manage their use. The first is that many providers believe failure is not an option. This manifests by trying multiple agents after a patient has failed one therapy or continuing therapy even though the benefit has been minimal. The second concept is stacking therapies. Stacking occurs when a patient is a partial responder to one agent. A second agent is added to the first agent instead of discontinuing the first agent. The other issue, which must be understood, is the biologic development pipeline. The largest area of growth, based on the agents under development, is going to be in oncology.

Awareness on the part of those who manage health plans is the most important tool to prevent or limit the seven creeps. Other tools include the use of case management, prior authorization, a specialty PBM, and strict oversight that limits use to evidence based indications. Experts, individually or through Centers of Excellence, should be used to handle appeals and provide guidance where necessary. Focused intervention with certain providers who seem to be moving in the direction of overusing biologics may be needed. One additional tool is the use of protocols for step therapy. There needs to be a level of expertise within the plan to manage patients on biologic injectable therapy. If the plan does not have it, which is permissible, the expertise has to be rented or bought. Lastly, managing the expectations of the consumers, the physicians and patients, is important. The plan needs to educate their consumers on the requirements for biologic coverage.

Conclusion

Although biologics have efficacy in inducing short-term remissions in Crohn's disease, the response declines over time and side effects occur. Additionally, these agents are not beneficial if the patient does not take them. A team approach with the physician, the health plan, and the case manager can ensure that these agents are used correctly and appropriately. Managed care has to be aware of the issues leading to increased biologic use to effectively manage this category of medication. **JMCM**

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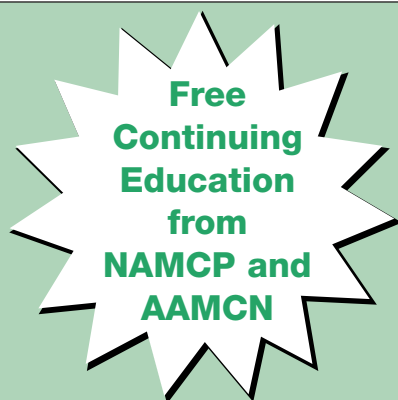
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